case report

Ocular metastasis of colorectal cancer: An uncommon presentation of a common malignancy

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Abstract Approximately 20% of patients with colorectal cancer have metastatic disease at time of diagnosis, and another 25–35% develop metastases during the course of their disease. Liver, peritoneum, and lungs are the most common sites of metastases. We report the case of a 60-year-old female who presented with ocular metastasis 4 years after her initial curative-intent treatment for T3N1M0 rectal adenocarcinoma. After local eye radiation therapy, she received palliative systemic chemotherapy and enjoyed a good quality of life for 32 months before succumbing to progressive disease. Ocular metastasis of colorectal cancer is rare. When present, it usually occurs in the setting of diffuse hematogenous spread. In addition to local therapy, systemic chemotherapy should also be considered.

KEYWORDS: Colorectal cancer; Ocular metastasis

INTRODUCTION

Colorectal cancer is the third most common cause of cancer death in the United States.[1] Approximately 20% of patients with colorectal cancer have distant metastases at diagnosis, and another 30% develop metastases during their disease course.[2–4] The most common sites of metastases for colorectal cancer include liver (77%), peritoneum (25%), and lungs (22%).[5]

Primary intraocular neoplasia is relatively uncommon; uveal melanoma is the most common primary ocular malignancy among adults, with an annual incidence rate of about six per million.[6] However, intraocular metastases occur more frequently with primary breast or lung cancers.[7,8] Histology, other than adenocarcinoma, is rare. The choroid is the most common ocular site of metastases, accounting for more than 80% of cases. In this case report, we present a patient with choroidal metastasis from *KRAS* wild-type rectal cancer which occurred 4 years after her primary diagnosis.

CASE REPORT

A 60-year-old African-American female with no prior ocular history presented for ophthalmologic examination in July 2010, following 2 weeks of visual disturbance in the left eye. She initially described a 'small flickering light' in the periphery of the left temporal visual field. This was followed by worsening visual acuity and the development of a floating 'black' scotoma in the temporal half of the left visual field.

Ocular examination noted a visual acuity of 20/40 in the right eye and 20/400 in the left. Fundoscopic examination of the left eye revealed a 15 mm × 15 mm creamy yellow amelanotic choroid mass extending supranasally form the optic disk into the superior nasal periphery. The lesion had a nodular appearance at its edges and had 180° contact with the optic nerve. It involved the macular region as well. Overlying subretinal fluid was noted centrally and inferiorly, suggesting exudative retinal detachment (Figure 1). Examination of the right eye revealed no choroidal lesions. B-scan ultrasound demonstrated a

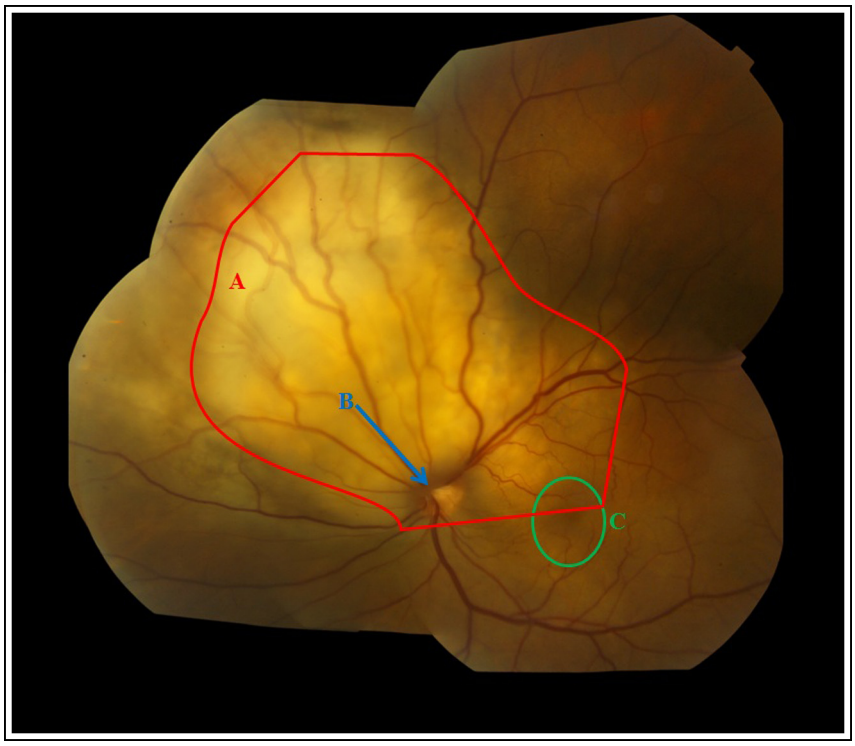

Figure 1. Amelanotic nodular choroid mass (A, encircled red) extending supranasally form the optic disc (B, pointed blue) and involving macula (C, encircled green).

solid mass with intermediate to high reflectivity and a height of 3.6 mm (Figure 2A). There was no extraocular extension. These findings were thought to be consistent with choroidal metastasis.

This patient had a history of rectal adenocarcinoma (T3N1M0), diagnosed in June 2006. She was treated with neoadjuvant capecitabine-based chemoradiation (5040 cGy over 5 weeks) followed by a laparoscopic abdominoperineal resection (APR) in September 2006, and three cycles of adjuvant capecitabine completed by December 2006. The surgical specimen revealed a well-differentiated adenocarcinoma extending to muscularis propria, and two of 11 lymph nodes were involved. The patient was lost to follow-up, but had no medical complaints until the current presentation.

After diagnosis of left eye choroidal metastasis, the patient underwent further staging work-up with positron emission and computed tomography (PET/CT) scan. This demonstrated multiple hypermetabolic nodules in the lungs, right adrenal gland, lumbar spine (L1), right sacrum and right inferior pubic ramus. Magnetic resonance imaging (MRI) of the brain was unremarkable. A fine needle aspiration (FNA) obtained from a lung nodule demonstrated adenocarcinoma cells positive for cytokeratin-20, CDX-2, and negative for cytokeratin-7 by immunohistochemistry, consistent with metastasis from a primary colorectal cancer. The *KRAS* gene exon 2 status was wild-type. Overall, the patient was feeling well without shortness of breath, cough or other systemic complaints, and the Eastern Cooperative Oncology Group (ECOG) performance status was 0.

With the goal of visual restoration, the patient was treated with radiation therapy to the posterior half of the left eye (3500 cGy over 14 fractions) in November 2010. Repeat ophthalmological and ultrasound examination demonstrated a partial regression. However, there was no improvement in her vision.

Following completion of radiotherapy to ocular metastasis, the patient began systemic chemotherapy in December 2010 with intravenous 5-fluorouracil (5-FU), leucovorin, oxaliplatin (FOLFOX) and bevacizumab (Avastin) in two-weekly cycles. CT scans after four cycles of chemotherapy demonstrated a partial response. Ophthalmologic examination at that time revealed a completely flat residual lesion (Figure 2B) with pigmentary changes. Of note, the patient reported slight improvement in her vision during the course of her chemotherapy. After 12

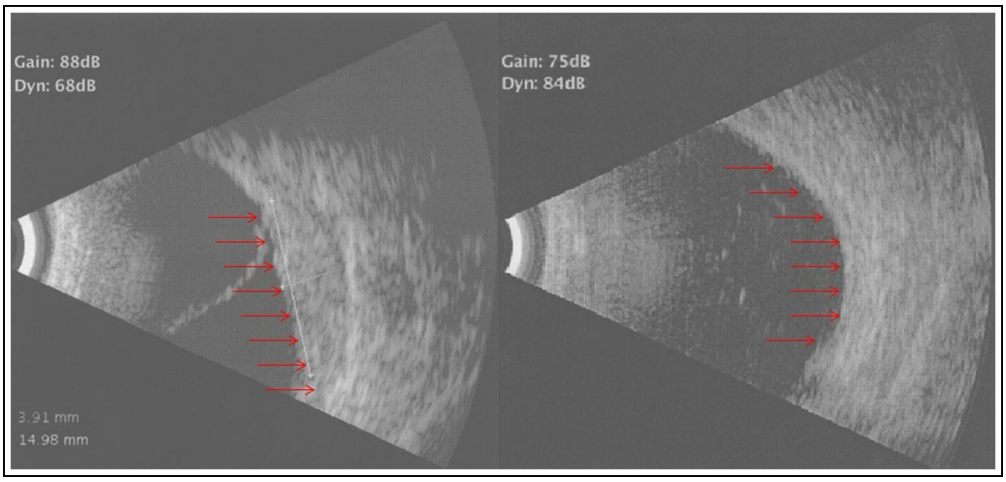

Figure 2. Ultrasound examination of left eye. (A) At initial presentation, a 3.6 mm solid mass with intermediate to high reflectivity was noted (red arrows), without any extraocular extension. (B) After completion of radiation and chemotherapy, complete flattening of lesion was noted (red arrows).

bi-weekly treatments (6 months), she developed a grade 3 infusion allergic reaction to oxaliplatin, and was continued on maintenance 5-FU and bevacizumab treatments. After 8 months of chemotherapy, the patient was noted to have disease progression upon restaging CT scans in August 2011. However, she did not report any deterioration in vision.

The patient decided to be treated with second-line systemic chemotherapy on a clinical trial (ECOG7208) with irinotecan, cetuximab and ramucirumab, a monoclonal antibody against vascular endothelial growth factor receptor-2 (VEGFR2), in two-weekly cycles. The patient had disease response on second-line therapy but required dose modifications due to irinotecan-induced myelosuppression (neutropenia); irinotecan was eventually discontinued during cycle 24. Following cycle 28, cetuximab and ramucirumab were also dose-reduced for skin toxicity (rash). The patient continued on treatment with cetuximab and ramucirumab until cycle 34 (January 2013), when she developed disease progression with increasing bone (spine), and new brain metastases. However, there was no evidence of progression of the ocular metastasis. Palliative radiation to T12–L2 vertebral bodies and whole brain radiation were administered. However, she continued to develop further symptomatic spine, bone and leptomeningeal metastases. The patient underwent palliative surgery with internal fixation of a right intertrochanteric femoral fracture. Her performance status continued to decline, with alterations of mental status. After detailed discussion with family, hospice care was initiated and patient died in February 2013.

DISCUSSION

The current case illustrates a rare site of metastasis for colorectal cancer (CRC). It is now established that metastasis is the most common cause of ocular malignancy. Gastrointestinal tract cancers account for only about 4% of ocular metastasis.[7,9] Few series have specifically described characteristics of ocular metastasis of CRC. Utilizing OVID and MEDLINE, we conducted a literature search to identify previously reported cases of CRC with ocular metastasis that describe the clinical characteristics of this uncommon group. Keywords used for the literature search included 'colorectal neoplasms', 'metastasis' and 'eye neoplasms'. Eight previously published cases were retrieved (including one patient each with orbit and anterior eye chamber metastases).[10–17] The case of a patient with rectal cancer metastatic to the anterior chamber of the eye (between cornea and the iris) was published as part of a case series, but details of the individual patient were not available.[17] Nevertheless, the authors emphasize the poor prognosis among the 26 patients with various malignancies metastatic to the anterior segment of the eye (5.4 months), compared to those with orbit metastases (15.6 months). Characteristics and outcomes of the remaining seven patients and the patient presented in the current report are summarized in Table 1.

'Visual disturbance' was the presenting symptom among all CRC patients with intraocular metastasis. In only one patient, the primary malignancy (CRC) was diagnosed after the onset of visual disturbance

Table 1. Summary of literature review of colorectal cancer with ocular metastasis.

	Age (yr)	Sex	Time from initial Dx	Initial site	Other mets	Ocular extent	O-Surg	O-RT	Chemo	Outcome
Khawaja et al.	60	F	4 yr	Rectum	Yes	Choroid	No	Yes	FOLFOX-B	Died at 32 mo
Apte et al.	39	M	3 mo	Cecum	Yes	Retina	Excision	Yes	FOLFIRI	Alive at 7 mo
Howard et al.	63	M	3 yr	Ascending colon	Yes	Retina, choroid, orbit	Enucl	No	No	Died at 16 mo
Kennedy et al.	51	M	–	Rectosigmoid	No	Choroid, macula	Enucl	No	No	Died at 9 mo
Lin et al.	43	M	8 yr	Sigmoid	Yes	Choroid	No	No	i-B	Died at 4 mo
Kuo et al.	65	F	20 mo	Colon	Yes	Choroid	No	No	i-B	Alive at 5 mo
Ward et al.	52	F	NA	Colon	Yes	Choroid b/l	No	No	No	Diet at 1 mo
Hisham et al.	32	F	10 mo	Rectum	Yes	Orbit	No	Yes	No	Died at 2 mo

M: male; F: female; Yr: years; Mo: months; Dx: Diagnosis; NA: not available; Mets: metastasis; b/l: bilateral; O-Surg: ocular surgery; Enucl: enucleation; O-RT: ocular radiation therapy; B: bevacizumab; i-B: intravitreous bevacizumab.

and no other sites of metastases were found.[12] All of the other patients had a known history of colorectal cancer and had developed systemic metastases by the time visual disturbance developed. Two patients with treated only with eye enucleation and no other treatment, and died with systemic progression within 9 and 16 months, respectively.[11,12] Two patients were treated with intravitreous bevacizumab only.[13,14] One of these patients, with bilateral choroid metastasis, had significant response in one eye while the tumor continued to progress in the other eye, presumably due to massive exudation hindering bevacizumab from reaching the metastatic tumor. This patient died 4 months after his ocular presentation.[13] The other patient treated with intravitreous bevacizumab also received radiation therapy for brain metastasis, and was alive after 5 months of follow-up.[14] One patient underwent excision of the retinal mass followed by palliative ocular radiation and systemic chemotherapy with 5-FU, leucovorin and irinotecan (FOLFIRI), and was alive after 7 months of follow-up.[10] One patient was offered palliative ocular radiotherapy but declined any treatment, and died after 1 month.[15] Another patient received palliative radiotherapy but died of intestinal obstruction 2 months later.[16]

The patient reported here was initially treated with local radiation therapy for ocular metastasis followed by systemic chemotherapy, and enjoyed a good quality of life for 32 months before succumbing to progressive disease, with bone, brain, and leptomeningeal metastases. This report describes the longest follow-up reported in a patient with ocular metastasis of colorectal cancer and therefore provides a unique opportunity to learn about the natural history of this rare presentation.

Ocular metastases occur in the context of diffuse hematogenous spread of CRC, and are most frequently accompanied by other systemic metastases. The addition of systemic chemotherapy to local treatment should theoretically yield better outcomes, and the current review of literature appears to support this approach. One patient, described in the literature, who did not have any other evidence of distant metastases, received only local therapy (enucleation) and died after 9 months, presumably from generalized disease progression. On the other hand, two patients who received systemic chemotherapy had other known metastases; both of these were alive at the end of their respective follow-up period.

To our knowledge, the current case is the first report of systemic bevacizumab use in the setting of ocular metastasis of CRC. Use of intravitreous bevacizumab is common for a variety of ocular conditions, including exudative age-related macular degeneration, diabetic retinopathy, ocular veno-occlusive disease and primary or metastatic ocular malignancies.[18] As discussed above, the two patients who received intravitreous bevacizumab for CRC with ocular metastasis had mixed results.

In conclusion, ocular metastasis of CRC is rare and occurs as part of generalized metastasis to multiple organ sites. The addition of systemic chemotherapy to local treatment of ocular disease may improve overall outcomes.

CONFLICT OF INTEREST

None declared.

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